REMARKS

To expedite prosecution, Applicants have amended claim 1 to a preferred embodiment, namely to measuring at least two target nucleic acid sequences in one reaction. The dependent claims have been amended to comply with this amendment. Support for this amendment can be found throughout the specification, for example, in paragraphs [0031] and [0035].

To expedite prosecution, Applicants have further amended claim 1 to combine with it the subject matter of claim 4. Thus, claim 4 has been cancelled.

Accordingly, Applicants submit that no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicants have added new claims 10-15. Support for this amendment can be found throughout the specification, for example, in paragraphs [0031], [0035], and [0052]-[0054]. Accordingly, no new matter has been introduced by the new claims and their entry is respectfully requested.

Claims 1-8 were rejected under 35 U.S.C. §112, second paragraph.

Applicants submit that the rejection be withdrawn for the following reasons.

Applicants have amended claim 1 as described, *supra*. Accordingly, Applicants respectfully submit that all claims now comply with the 35 U.S.C. §112, second paragraph, and request that the rejection of claims 1-8 under 35 U.S.C. §112, second paragraph be withdrawn.

Claims 1, 3, 5, 6 and 7 were rejected under 35 U.S.C. §102(b) as anticipated by Bunn et al. (U.S. Patent No. 5,213,961).

Applicants submit that the rejection be withdrawn for the following reasons.

Claim 1 has been amended to expedite prosecution of a preferred embodiment, namely quantification of at least two nucleic acid sequences using mass spectrometry. Bunn does not teach or suggest that more than one target nucleic acids can be measured in a same reaction. Additionally, Bunn does not use a second quantifying step. Further, Bunn does not teach or suggest quantification using mass spectrometry.

Accordingly, Applicants respectfully submit that the rejection of claims 1, 3, 5, 6, and 7 under 35 U.S.C. §102(b) be withdrawn.

Claims 1, 3, and 6 were rejected under 35 U.S.C. §102(b) as anticipated by Becker et al.

Applicants submit that the rejection be withdrawn for the following reasons.

Claim 1 has been amended to expedite prosecution of a preferred embodiment, namely quantification of at least two nucleic acid sequences using mass spectrometry. Becker does not teach or suggest that more than one target nucleic acids can be measured in the same reaction. Further, Becker does not teach or suggest a subsequent step of quantification using mass spectrometry.

Accordingly, Applicants respectfully submit that the rejection of claims 1, 3, and 6 under 35 U.S.C. §102(b) be withdrawn.

Claim 2 was rejected under 35 U.S.C. §103(a) as obvious over Bunn in view of Carroll et al., (U.S. Patent No. 5,906,744) ("Carroll").

Applicants respectfully submit that the rejection be withdrawn for the following reasons.

Claim 1 has been amended as described, *supra*. As discussed, *supra*, Bunn does not teach or suggest the claimed invention. The addition of Carroll does not overcome this deficiency. Carroll does not teach or suggest measuring more than one nucleic acid target in a sample using mass spectrometry. Accordingly, the combination of Bunn with Carroll does not teach or suggest a method of measuring the amount of at least two target nucleic acids in a sample. Moreover, the combination of the references does not teach or suggest using mass spectrometry. Therefore, Applicants respectfully submit that the rejection of claim 2 under 35 U.S.C. §103(a) as obvious over Bunn in view of Carroll be withdrawn.

Claim 2 was further rejected under 35 U.S.C. §103(a) as obvious over Becker et al. as cited in the IDS ("Becker) in view of Carroll.

Applicants submit that the rejection be withdrawn for the following reasons.

Applicants have amended claim 1 as described, *supra*. Also, as discussed, *supra*, Becker does not teach or suggest quantifying at least two target nucleic acid sequences in a same sample reaction. Moreover, Becker does not teach use of mass spectrometry. As described, *supra*, Carroll does not overcome these deficiencies. Therefore, Applicants respectfully submit that the rejection of claim 2 under 35 U.S.C. §103(a) as obvious over Becker in view of Carroll be withdrawn.

Claims 4, 5, 7, and 8 were rejected under 35 U.S.C. §103(a) as obvious over Becker in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pp. 12097-12102) ("Amexis").

Applicants respectfully submit that the rejection be withdrawn for the following reasons.

Applicants have amended claim 1 and cancelled claim 4as described, *supra*.

Applicants respectfully disagree with the Examiner and submit that one would not have been motivated to combine Amexis with Becker to arrive at the method as claimed for the following reasons.

The Examiner contended that because the method as described by Becker is based on detection of radioactive label, one would have been motivated to use a non-radioactive method of Amexis. Such a motivation would have led a skilled artisan to look for other types of labels, such as fluorescent or enzymatic labels that would have been directly applicable to the gel electrophoretic method taught by Becker. There is nothing in Amexis that would direct one skilled in the art to choose to combine it with a totally different type of method, particularly a method that would require additional steps. In contrast, Amexis presents a method of detecting the absolute peaks as accurate and simple method to detect the presence or absence and the relative amount of virus mutants in a sample (see, e.g. page 12102, first col.). There is no reason to use a different standard. Why would the skilled artisan want to make the system more complicated, if the system is taught as working well for its purpose? Amexis shows detecting virus strains and their relative amount in a sample. However, as taught in the present specification, measurement of the absolute signals is not accurate enough (see, e.g., par. [0048] of the specification), for all applications. Only in impermissible hindsight, is one directed to think about making the method of Amexis more accurate and suitable for quantitation of, e.g., gene expression patterns or changing from a label system of detection to mass detection.

There are many differences between a direct spectrometric measurement and a radioactive measurement of gel-separated nucleic acids. Without the teaching that is provided in the present specification, for example at pars. [0049] and [0050], it would not have been evident, that more than one template could be analyzed accurately using mass spectrometric analysis when adding multiple nucleic acids into the mix, i.e., the at least two standard nucleic acids as required by the present claims. Certainly, this expectation does not come from the gel

electrophoresis analysis of Becker, because as one skilled in the art well knows, it is nearly impossible to analyze a large mix of short nucleic acids using such separation techniques.

Moreover, even assuming, *arguendo*, that there would have been motivation to combine the references, Applicants submit that the combination of Becker with Amexis does not teach or suggest the presently amended claims. The method of Becker describes measuring the amount of only one nucleic acid at a time in a sample. Combining Amexis's teaching of using mass spectrometry to measure nucleic acids does not result in a method where one uses at least two standard nucleic acids to simultaneously determine the amount of at least two target nucleic acids in a same sample.. Accordingly, the combination of Becker with Amexis does not teach or suggest all the elements of the amended claims.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. At minimum, the amendments to the claims will reduce the issues on appeal.

Early and favorable action is requested. Examiner is encouraged to contact the undersigned attorney should she have questions regarding the application.

In the event that any additional fees are required, the PTO is authorized to charge Nixon Peabody LLP deposit account No. 19-2380.

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Respectfully submitted,

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